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RESEARCH TRIANGLE PARK, NC 27709

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte MICHAELA ARNDT,
MELVYN LITTLE,
SERGEY KYPRIVANOV,
JURGEN KRAUSS,
and
MICHAEL PFREUNDSCHUH,
Appellants

Appeal 2008-2106
Application 10/049,404[1]
Technology Center 1600

Decided: 6 May 2008

Before TEDDY S. GRON, CAROL A. SPIEGEL, and
TONI R. SCHEINER, *Administrative Patent Judges.*

SPIEGEL, *Administrative Patent Judge.*

DECISION ON APPEAL

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[1] Application 10/049,404 ("the 404 application"), filed 5 August 2002, is said to be the national phase (35 U.S.C. § 371) of international application PCT/DE00/02589, filed 2 August 2000. PCT/DE00/02589 is said to claim priority benefit of German Application 199 37 264.0, filed 6 August 1999. The real party in interest is said to be Deutsches Krebsforschungszentrum Stiftung des Offentlichen Rechts (Brief on Appeal for U.S. Patent Application No. 10/049,404 filed 23 March 2007 ("App. Br.") at 4).

I. Statement of the Case

This is an appeal under 35 U.S.C. § 134 from a final rejection of claims 1-6, 15, 19, and 22. Claims 7-14, 16-18, 20, and 21, the only other pending claims, have been withdrawn from consideration. We have jurisdiction under 35 U.S.C. § 6(b) (2002). We AFFIRM.

The subject matter on appeal is directed to an F_v antibody[2] construct which specifically binds CD30 antigen, such as found on the surface of Hodgkin cells (HD cells), with one arm and CD16 antigen, such as found on the surface of natural killer cells[3] (NK cells), with its second arm, thereby recruiting NK cells to specific tumor cells, e.g., HD cells. Claims 1 and 22 are illustrative and read (App. Br. Claims Appendix at 1-2):

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[2] A basic antibody molecule is formed of four peptide chains -- two identical longer "heavy" chains and two identical shorter "light" chains. Disulfide bonds link the light chains to the heavy chains in a "Y" configuration with three regions: a stem and two arms connected to a flexible hinge region. The lower portions of the two heavy chains form the lower stem or Fc region. The two light chains and the upper portions of the two heavy chains form the two arms. The arms contain variable amino acid sequences in regions (domains) of each constituent heavy and light chain which determines what antigen the antibody will bind (F_{ab} or fragment, antigen-binding). F_v fragments are heterodimers formed from a variable heavy chain domain and a variable light chain domain and are the small functional units of antibodies that maintain the binding and specificity of the whole antibody.

[3] NK cells are large granular lymphocytes that have the ability to lyse other cells, such as tumor cells and virally infected cells, without prior sensitization. NK cells are characterized by their cell surface markers CD16 and CD 56. CD16 (also known as the FcγIIIA receptor) is a Fc receptor for IgG and, thus, NK cells are able to lyse selectively those cells which are coated with antibodies (Antibody-Dependent Cell-Mediated Cytoxicity or ADCC). See e.g., HENRY'S CLINICAL DIAGNOSIS AND MANAGEMENT BY LABORATORY METHODS, McPherson and Pincus, eds., 21st edition, Saunders Elsevier, Philadelphia, PA (2007), pp. 790-791.

> 1. A F_v antibody construct having variable domains for CD16 and a CD30 but no constant domains and inducing a regression of Hodgkin's disease *in vivo*.
>
> 22. The F_v antibody construct according to claim 1, wherein said F_v antibody is capable of inducing a more intense lysis of CD30 carrying cells *in vitro* than bimAbHRS-3/A39 (DSM ACC2142).

The Examiner has relied upon the following references as evidence of unpatentability:

> Hartmann et al., "Treatment of Refractory Hodgkin's Disease With an Anti-CD16/CD30 Bispecific Antibody," *Blood*, Vol. 89, No. 6 (March 15, 1997): 2042-2047 ("Hartmann 1997").
>
> Hartmann et al., "Anti-CD16/CD30 Bispecific Antibodies as Possible Treatment for Refractory Hodgkin's Disease," *Leukemia and Lymphoma*, Vol. 31 (1998): 385-392 ("Hartmann 1998").
>
> Holliger et al., "'Diabodies': Small bivalent and bispecific antibody fragments," *Proc. Natl. Acad. Sci. USA*, Vol. 99 (July 1993): 6444-6648 ("Holliger").

The issues on appeal[4] are whether

(a) claim 22 is indefinite under 35 U.S.C. § 112, ¶2;

(b) claim 22 lacks enablement under 35 U.S.C. § 112, ¶1;

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[4] The final rejections of claims 1-6, 15, 19, and 22 under 35 U.S.C. § 112, ¶1 (written description) and under 35 U.S.C. § 102(a) as anticipated by Arndt et al. (*Blood*, Vol. 94 (1999):2562-2568) were withdrawn by the Examiner in an Advisory Action mailed 7 November 2006 (App. Br. at 5; Examiner's Answer mailed 10 July 2007 ("Ans.") at 2).

(c) claims 1-5 and 15 are anticipated under 35 U.S.C. § 102(b) by Hartmann 1997; and

(d) claims 1-6, 15, 19, and 22 would have been obvious under 35 U.S.C. § 103(a) over Hartmann 1998 in view of Holliger.

II. Discussion

A. Rejection under § 102(b)

Claims 1-5 and 15 stand rejected under 35 U.S.C. § 102(b) as anticipated by Hartmann 1997 (Ans. at 5). Appellants argue that since claim 1 is not anticipated by Hartmann 1997, claims 2-5 and 15 are also not anticipated by Hartmann 1997 (App. Br. at 13). Therefore, all claims stand or fall with claim 1. 37 C.F.R. § 41.37(c)(1)(vii).

Anticipation requires disclosure of each and every claim limitation in a single prior art reference, either explicitly or inherently. *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999).

Hartmann 1997 discloses treating fifteen patients with Hodgkin's disease with a murine bispecific monoclonal antibody (bimAb) HRS-3/A9, which binds to the CD30 antigen expressed on the surface of the Hodgkin tumor cells with one arm and to the CD16 receptor expressed on the surface of NK cells with the other arm, to induce specific lysis of $CD30^+$ tumor cells in a phase I/II clinical trial (Hartmann 1997 at 2042). One complete and one partial remission, as well as four minor or mixed responses, were attained (*id.*). Nine patients developed a human antibody response against the murine antibody (i.e., human anti-mouse antibodies or HAMAs) after four weeks of treatment (*id.* at 2044). Hartmann 1997 states that "this problem [HAMAs] should be resolvable by the construction of less immunogenic

bispecific single-chain antibodies or so-called 'diabodies'" (*id.* at 2046, col. 2, endnotes omitted).

Pointing to *In re Petering*, 301 F.2d 676 (CCPA 1962), the Examiner essentially argues that a skilled artisan would have instantly envisaged the claimed bispecific F_v antibody construct from Hartmann 1997's teaching of HAMA side-effects in treatments with murine anti-CD16/CD30 bispecific antibody, e.g., bimAb HRS-3/A9. Treatment problems should be resolvable using less immunogenic bispecific single chain antibodies or diabodies. [Ans. 12.]

However, a mere suggestion that a problem "should be resolvable" by pursuing a generic group of bispecific single-chain antibodies or so-called "diabodies" is insufficient to establish possession. In *Petering*, the prior art disclosed a limited number of specific preferences from a specifically defined group of isoalloxazines. *Petering*, 301 F.2d at 677. To wit, *Petering* expressly spelled out a definite and limited class of compounds that allowed a person of ordinary skill in the art to at once envisage each member of the limited class. *Id.*, 301 F.2d at 681-82. Here, Hartmann 1997 does not disclose a definite and limited class of F_v constructs. For example, Hartmann 1997 does not disclose what type of linker must be used to connect variable heavy and light chain CD16/CD30 antigen-binding domains of bispecific single chain antibodies, e.g., so that the linker does not interfere with antigen binding, or whether interchain disulfide bonds need to be introduced into the "diabodies" to maintain the structural relationship between the two antigen binding domains that exists in the whole bimAb HRS-3/A9 antibody. Thus, unlike *Petering*, Hartmann 1997 does not expressly spell out a definite and limited class of bispecific F_v constructs that

allows a person of ordinary skill in the art to at once envisage each member of the limited class. While Hartmann 1997 suggests the pursuit of bispecific CD16/CD30 single chain antibodies or so-called "diabodies" to resolve side-effects that occur due to administration of a murine antibody (bimAb HRS-3/A9) to a human, Hartmann 1997 does not reasonably describe an F_v antibody construct having variable domains for CD16 and CD30, but no constant domain, that would have been expected to induce a regression of Hodgkin's disease *in vivo* as recited in claim 1.

Accordingly, based on the foregoing, we REVERSE the rejection of claims 1-15 and 15 under § 102(b) over Hartmann 1997.

B. Rejection under § 103(a)

Claims 1-6, 15, 19, and 22 stand rejected under 35 U.S.C. § 103(a) as obvious over Hartmann 1998 in view of Holliger (Ans. at 6). Appellants argue that since claim 1 is not obvious over Hartmann 1998 in view of Holliger, claims 2-5 and 15 are also not obvious over Hartmann 1998 in view of Holliger (App. Br. at 17). Appellants only separately argue the patentability of claim 22 (Reply Br. at 16-18) in response to the Examiner's first substantive discussion of the obviousness of the limitation "capable of inducing a more intense lysis of CD30 carrying cells *in vitro* than bimAbHRS-3/A9" recited in claim 22 (Ans. 7). Therefore, we shall decide the patentability of claims 1-6, 15, 19, and 22 with reference to claims 1 and 22. 37 C.F.R. § 41.37(c)(1)(vii).

A claimed invention is not patentable if it would have been obvious to a person having ordinary skill in the art. 35 U.S.C. § 103(a); *KSR Int'l Co. v. Teleflex, Inc.*, 127 S.Ct. 1727, (2007); *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966). Facts relevant to a determination of obviousness

include (1) the scope and content of the prior art, (2) any differences between the claimed invention and the prior art, (3) the level of ordinary skill in the art, and (4) relevant objective evidence of obviousness or non-obviousness. *KSR*, 127 S.Ct. at 1734; *Graham*, 383 U.S. at 17-18. "If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *KSR*, 127 S.Ct. at 1740. Furthermore, optimization flows from the "normal desire of scientists or artisans to improve upon what is already generally known." *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003); *In re Aller*, 220 F.2d 454, 456 (CCPA 1955). "[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." *In re Boesch*, 617 F.2d 272, 276 (CCPA 1980).

The disclosure of Hartmann 1998 is similar to that of Hartmann 1997. Hartmann 1998 discloses treating fifteen patients with Hodgkin's disease with a murine bispecific monoclonal antibody (bimAb) HRS-3/A9, which binds to the CD30 antigen expressed on the surface of the Hodgkin tumor cells with one arm and to the CD16 receptor expressed on the surface of NK cells with the other arm, to induce specific lysis of $CD30^+$ tumor cells in a phase I/II clinical trial (Hartmann 1998 at 385-386). One complete and one partial remission, as well as four minor or mixed responses, were attained (*id.* at 386). At least six patients developed a human antibody response against the murine antibody (i.e., human anti-mouse antibodies or HAMAs) after five weeks of treatment (*id.* at 388, 390). Hartmannn 1998 concludes:

> in patients with no change in tumor size we attempt to give a second BiMoAb cycle after prestimulation with . . . IL-2 . . . and GM-CSF. . . Moreover, by using modified BiMoAb application schedules retreatment seems to be possible in the majority of patients even after increase of

> circulating NK cells and other lymphocyte populations by cytokines, therefore expanding the treatment options until humanized or recombinant bispecific antibodies will become available[25, 26]. [Hartmann 1998 at 391.]

Holliger is the reference 25 cited in Hartmann 1998 at page 391.

According to Holliger, bispecificity allows the cross-linking of two antigens, for example, in recruiting cytoxic T cells to mediate killing of a tumor cell (Holliger at 6444, col. 1). However, it is often preferable to use antibody fragments instead of whole antibodies because the Fc region of an antibody can lead to illegitimate targeting to cells expressing Fc receptors (*id.*). Holliger discloses making constructs for the expression of bispecific and bivalent fragments of two different antibodies or "diabodies" (Holliger at abstract and 6445) by linking the variable region of the heavy chain (V_H) from one antibody to the variable region of the light chain (V_L) from the other to create two "cross-over" chains, V_HA-V_LB and V_HB-V_LA, that are coexpressed in the same cell and associate to form dimers with two antigen binding sites on the same molecule (Holliger at 6646-6647). According to Holliger, fragments linked "with 5- and 15-residue linkers had similar binding affinities to the parent antibodies, but a fragment with the V_H domain joined directly to the V_L domain was found to have slower dissociation kinetics and an improved affinity for hapten" (Holliger at 6646, abstract). Further according to Holliger, since diabodies are similar in size to antibody Fab fragments, they should penetrate tumors and be cleared from the serum more easily than whole antibodies (Holliger at 6448, col. 1).

The Examiner found that Hartmann 1998 teaches that bispecific anti-CD16/CD30 antibody HRS-3/A9 is a murine IgG antibody useful for

immunotherapy. It can induce HAMAs. To remedy the problem, Hartmann 1998 suggests using small bivalent and bispecific antibody fragments made in accordance with prior art teaching, with citation of, and express reference to, Holliger (Ans. at 14). The Examiner concluded that it would have been obvious to make an antiCD16/CD30 F_v construct lacking Fc domains with a reasonable expectation that it would successfully treat human Hodgkin's lymphoma in view of Hartmann 1998's successful use of the whole murine anti-CD16/CD30 antibody HRS-3/A9 to treat Hodgkin's lymphoma and Hartmann 1998's suggestion to use recombinant bispecific antibodies taught by Holliger to overcome the major obstacle Hartmann 1998 teaches that HAMAs (Ans. at 7-8 and 14). The Examiner further concluded that it would have been obvious to make an antiCD16/CD30 F_v construct lacking Fc domains because it was well known in the art that the use of F_v constructs instead of whole antibodies avoids illegitimate targeting to cells expressing Fc receptors and that F_v constructs can facilitate tumor penetration, see e.g., Holliger at 6444 and 6448 (Ans. at 7).

As to claim 22, the Examiner concluded that one of ordinary skill in the art would have reasonably expected an antiCD16/CD30 F_v construct lacking Fc domains to induce more intense lysis of CD30 carrying cells *in vitro* in view of Holliger's teaching that diabodies have increased antigen affinity vis-à-vis the parent antibody (Ans. 7).

Appellants argue that neither Hartmann 1998 nor Holliger are anticipatory references (App. Br. 15) and, since Holliger does not discuss cytotoxicity and Hartmann 1998 does not teach or suggest how to switch from immunotherapy using whole antibodies to immunotherapy using other, i.e., recombinant bispecific, antibodies, one of ordinary skill in the art would

have had neither the motivation to combine Hartmann 1998 and Holliger nor a reasonable expectation of success in doing so (App. Br. 15-16).

Appellants' claims stand rejected in view of the combined teachings of Hartmann 1998 and Holliger under § 103(a), not under § 102. It is improper to attack references individually where, as here, the rejection is based upon the teachings of a combination of references. *In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986); *In re Keller*, 642 F.2d 413, 425 (CCPA 1981).

Here, Hartmann 1998 discloses using an immunological "bridge," murine bispecific monoclonal antibody HRS-3/A9, between a natural killer cell, a $CD16^+$ cell, and a Hodgkin's tumor cell, a $CD30^+$ cell, to recruit a killer for the tumor (Hartmann 1998 at 385-86). Hartmann 1998 teaches that a major obstacle to prolonged and repeated use of the "bridge" is the development of human antibodies to the murine bridge (Hartmann 1998 at 390). Hartmann 1998 directs one of ordinary skill in the art toward treatment of Hodgkin's disease with a recombinant bispecific antibody and directs the skilled artisan to Holliger for such recombinant antibodies. F_v antibody constructs are known improvements on whole antibodies in immunotherapies because they are less immunogenic and, therefore, would be less likely to induce HAMAs. Making and using F_v antibody constructs from parent antibodies would have been within ordinary skill in the art as shown by Holliger. Furthermore, Holliger teaches that F_v antibody constructs with 5- and 15-residue linkers had similar binding affinities to the parent antibodies and suggests that shorter linkers improve binding affinity (Holliger at abstract). Holliger cautions that constructs meant to bridge two

cells may require a longer linker because more flexibility in the construct may be needed (Holliger at 6448).

Appellants argue that Holliger fails to disclose F_v constructs with linkers that had higher binding affinities than the parent antibodies (Reply Br. at 16-17). In regard to claim 22 specifically, Appellants state, "[I]t was very surprising . . . that a F_v construct having a 9 amino acid linker (as in a working example of the present application) is capable of producing a more intense lysis of CD30 carrying cells *in vitro* than the parent bimAbHRS-3/A9 antibody" (Reply Br. at 17). Appellants further argue that since the Fc region of bimAbHRS-3/A9 is able to be bind to Fc receptors on NK cells, the parent antibody would be expected to activate more NK cells than an F_v construct which lacks an Fc region (Reply Br. at 17).

Since the F_v construct, like its parent antibody, is cross-linking two cells, NK cells and Hodgkin's tumor cells, as opposed to two soluble antigens, Holliger teaches that some flexibility in the F_v construct, e.g., in selecting the linker, may be required (Holliger at 6448). "[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." *Boesch*, 617 F.2d at 276. Appellants have not pointed to evidence of record showing unexpected results due to a select linker in the F_v construct, specifically a 9 residue linker. Further, even assuming *arguendo* that a whole antibody activates more NK cells than a derivative F_v construct, Appellants have not pointed to evidence showing that activating more NK cells *per se* results in more intense lysis of a target cell or that size differences between a whole antibody and an F_v construct have no effect. Attorney argument, absent supporting evidence, is entitled to

little, if any, weight. *Velander v. Garner*, 348 F.3d 1359, 1371, (Fed. Cir. 2003); *Meitzner v. Mindick*, 549 F.2d 775, 782, (CCPA 1977).

Based on the foregoing, we AFFIRM the Examiner's rejection of claims 1-6, 15, 19, and 22 under § 103(a) over Hartmann 1998 and Holliger.

C. Rejection under § 112, ¶1 (enablement)

Claim 22 stands rejected under 35 U.S.C. § 112, ¶1 (enablement).

According to the Examiner, since comparison to the antibody bimAbHRS-3/A9 is required to practice the invention of claim 22, the antibody must have been known, readily available to the public, and/or obtainable by a repeatable method set forth in the specification (Ans. at 4).

The Examiner does not dispute that page 2, ¶2, of Appellants' 404 specification was amended on June 13, 2006 to insert "(DSM deposit number ACC 2142; described in U.S. Patent 5,643,759 ("the 759 patent") issued July 1, 1997 to Michael Pfreundschuh)" after "bimAbHRS-3/A9 (Amendment filed June 13, 2006 at 3) (Ans. at 11). However, the Examiner argues that the 759 patent has expired. Therefore, the public availability of bimAbHRS-3/A9 is in question (Ans. at 11).

There is no dispute that the hybridoma producing monoclonal antibody bimAbHRS-3/A9 was deposited with the DSM depository (Deutsche Sammulung Von Mikroorganismen Und Zellkulturen GmbH) in accordance with 37 C.F.R. § 1.801 et seq. According to 37 C.F.R. § 1.802, "[o]nce deposited in a depository complying with these regulations, a biological material will be considered to be readily available. . . ." Therefore, bimAbHRS-3/A9 would have been readily available to the public at the time Appellants filed their patent application. Thus, we REVERSE the rejection of claim 22 under § 112, ¶1.

D. Rejection under § 112, ¶2 (definiteness)

"A claim is indefinite if, when read in light of the specification, it does not reasonably apprise those skilled in the art of the scope of the invention." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1342 (Fed. Cir. 2003).

According to the Examiner, claim 22 is indefinite in reciting that the claimed F_v construct "is capable of inducing *a more intense lysis* of CD30 carrying cells *in vitro* than bimAbHRS-3/A9" for three reasons. First, "more intense" is a relative term which is not defined in Appellants' specification. Second, the NK cells, which the claimed F_v construct and bimAbHRS-3/A9 "bridge" or "recruit" to the CD30 carrying cells, lyse (kill) the CD30 carrying cells. Third, since the F_v construct does not have an Fc region, it is smaller than whole antibody bimAbHRS-3/A9. Therefore, a 1 µg of F_v construct would been expected to be more effective in recruiting NK cells than 1 µg of bimAbHRS-3/A9 because the F_v construct would have more antigen binding sites/µg than an equal weight of whole antibody bimAbHRS-3/A9. [Ans. 3 and 9-10]

The plain language of claim 22 appears clear on its face, and the Examiner has not adequately explained why one of ordinary skill in the art would not have reasonably understood the metes and bounds of claim 22. The Examiner has not cited evidence establishing that "inducing" is limited to "causing directly" as opposed to "stimulating." The Examiner has not explained why one of ordinary skill in the art, in light of Appellants' specification (or from routine knowledge in the art), would not have understood that it is NK cells that actually lyse the CD30 carrying cells. Finally, positing why x molecules of F_v construct would have been expected

to induce more lysis of CD30 carrying cells than x molecules of bimAbHRS-3/A9, does not explain why one of ordinary skill in the art would not have been reasonably apprised of the metes and bounds of claim 22 in light of Appellants' specification. Patentability rejections cannot be based on unsupported speculations and suppositions. *In re Steele*, 305 F.2d 859, 862-63 (CCPA 1962).

Accordingly, we REVERSE the rejection of claim 22 under § 112, ¶2, as indefinite.

III. Order

Upon consideration of the record, and for the reasons given, it is

ORDERED that the decision of the Examiner rejecting claim 22 under 35 U.S.C. § 112, ¶2 (definiteness), is REVERSED;

FURTHER ORDERED that the decision of the Examiner rejecting claim 22 under 35 U.S.C. § 112, ¶1 (enablement), is REVERSED;

FURTHER ORDERED that the decision of the Examiner rejecting claims 1-5 and 15 under 35 U.S.C. § 102(b) as anticipated by Hartmann 1997 is REVERSED;

FURTHER ORDERED that the decision of the Examiner rejecting claims 1-6, 15, 19, and 22 under 35 U.S.C. § 103(a) as obvious over Hartmann 1998 in view of Holliger is AFFIRMED; and,

FURTHER ORDERED that no time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a) (2006).

AFFIRMED

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PO BOX 14329
RESEARCH TRIANGLE PARK, NC 27709